Development of Pediatric Vaccine Recommendations and Policies

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A significant decrease in each vaccine-preventable disease has occurred since the introduction of the respective immunizations now included in the recommended childhood immunization schedule. The process through which a vaccine must travel from development to approval and implementation is complex. Hurdles include receiving approval from several advisory committees, government agencies, and professional organizations. At each step in the process, data regarding safety, immunogenicity, and efficacy are evaluated continuously and rigorously. Once a vaccine is approved by the Food and Drug Administration (FDA) and incorporated into the recommended childhood immunization schedule, continuing issues include those that deal with supply, safety, effectiveness, and financing. The logistics of development and implementation of pediatric vaccine recommendations and policies are reviewed.

Vaccines are among the most effective means of preventing disease, disability, and death in infants, children, adolescents, and adults.[1,2] Declines exceed 95 percent for all diseases for which universal childhood immunization has been well implemented. Table 1 compares representative 20th century annual morbidity—generally prevaccine—with provisional 2001 morbidity and percent decrease for 9 vaccine-preventable diseases of childhood. The decrease for invasive pneumococcal disease in children is expected to occur after widespread use of conjugated pneumococcal vaccine in infants and children has been achieved. This vaccine was approved for use by the Food and Drug Administration (FDA) in February, 2000. The significant impact of vaccines on prevention of disease and reduction in morbidity and mortality is a complex process that is dependent upon the availability of safe and effective vaccines, programs to deliver vaccines to target groups, and acceptance and uptake of the vaccines.[3] In this review, the logistics of how pediatric vaccine recommendations and policies are developed, implemented, and monitored are discussed.

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Vaccine Development and FDA Approval

Testing Procedures

Each vaccine in the recommended childhood immunization schedule[4,5] progresses through similar testing procedures that include development, evaluation, approval, and recommendation (Figure 1). Before FDA licenses vaccines, they undergo preclinical development and testing. If preclinical testing is successful, a vaccine passes through 4 clinical phases, the first 3 of which occur prelicensure with permission from the FDA through an investigational new drug (IND) application (Table 2).[6] An application includes information about the vaccine, results of preclinical studies, the proposed clinical study, and information about the investigator. Phase 4 studies occur after the vaccine has been licensed. Phase 1 trials in humans include small numbers of volunteers and are designed primarily to identify problems of acute safety. Children are not enrolled in phase 1 trials. Phase 2 trials are designed to focus on dose range and immunogenicity, although safety outcomes also are collected. The number of volunteers increases in phase 2 trials, which may include children if they are targeted for eventual vaccination. Phase 3 trials examine vaccine efficacy as the main outcome and safety in larger numbers of participants. These trials usually are randomized, double-blinded, and placebo-controlled, and they may be conducted in different locations and provide substantial data upon which the licensing considerations are based. Phase 4 trials and postmarketing surveillance, which are conducted after licensure and expand the number of persons enrolled, can better define the frequency of uncommon adverse events in specific risk groups.

Phase 1, 2, and 3 trials often are conducted in the

Table 1. Comparison of 20th Century Prevaccine Annual Morbidity and Year 2001 Morbidity From Pediatric Vaccine-Preventable Diseases

Disease	*Annual Morbidity*		
	Prevaccine	*Provisional* Year 2001*	*Percent Decrease*
Diphtheria	175,885	2	100.0
Measles	503,282	108	100.0
Mumps	152,209	231	99.8
Pertussis	147,271	5,396	96.3
Polio (paralytic)	16,316	0	100.0
Rubella	47,745	19	100.0
Congenital rubella syndrome	823	2	99.8
Tetanus	1,314	27	97.9
Invasive *Haemophilus influenzae* type b disease (<5 yr)	20,000	183†	99.1
Invasive pneumococcal disease (<5 yr)	15,933†	14,382‡	9.7

*As of February 2002.
†Includes 61 cases with unknown serotype.
‡Projected cases; data are for year 2000.

network of the Vaccine Treatment and Evaluation Units (VTEUs), which are located in academic centers and which receive competitive funding from the National Institutes of Health (NIH). Phase 4 trials require larger numbers of participants and generally are conducted in managed care organizations where the potential for enrollment is excellent and automated data systems are available. The Center for Biologics, Evaluation, and Research (CBER) of the FDA regulates clinical trials.

FDA Advisory Committee

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) advises the FDA commissioner. The committee reviews and evaluates data concerning the safety, effectiveness, and appropriate use of vaccines and related biological products that are intended for use in the prevention, treatment, or diagnosis of human diseases. The committee also considers the quality and relevance of the research program of the FDA. VRBPAC consists of 15 members including the chair. The FDA commissioner or his/her designee selects members from authorities knowledgeable in immunology, molecular biology, virology, bacteriology, epidemiology, biostatistics, allergy, preventive medicine, infectious diseases, pediatrics, microbiology, and biochemistry. The Committee may include 1 technically qualified member who is a proponent of consumer interests. Members serve overlapping terms of 4 years.

Before deciding on licensure of a vaccine, CBER presents data to VRBPAC that evaluates the adequacy of the safety and efficacy data. VRBPAC members may recommend additional studies, including phase-4 studies. FDA licensure of a vaccine also consists of approving the package insert containing information about and guidance for use of the vaccine.

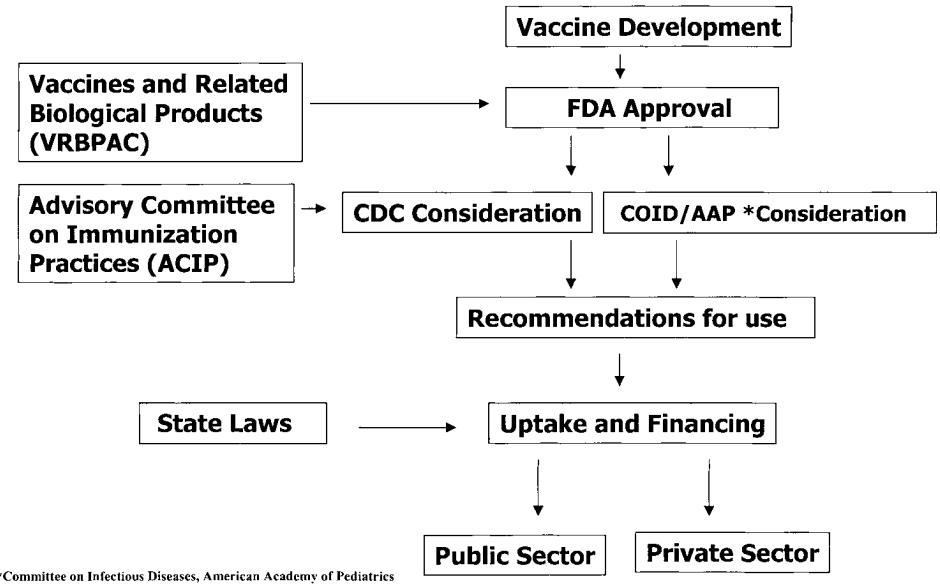

Figure 1. Development of pediatric vaccine recommendations and policies.

Table 2. Phases in Development of a Vaccine

Phase	*Studies*	*No. of Persons Usually Studied*	*Rate of Detectable Adverse Events*
1	Safety, immunogenicity	10-100	10-20%
2	Dose ranging, immunogenicity, safety	100-1000	1-10%
3	Efficacy, safety, immunogenicity	500-20,000	0.5-5%
4	Postlicensure studies, postmarketing surveillance	10,000-100,000 Millions	—

Vaccine Recommendations

Childhood immunization recommendations in the United States are developed independently by 2 groups, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) and the Committee on Infectious Diseases (COID) of the American Academy of Pediatrics (AAP). New vaccines are incorporated into the recommended childhood immunization schedule, which is updated each January to reflect changes in recommendations that have occurred during the previous year. The current harmonized schedule developed by the ACIP, the AAP, and the American Academy of Family Physicians (AAFP) specifies both the timing and the acceptable range of timing for each vaccine dose for universally recommended vaccines and for vaccines recommended for select populations.[4,5]

ACIP and COID members discuss recommendations for use of the vaccine before the FDA approves the vaccine, but the recommendations are not finalized until the FDA has licensed the vaccine. The recommendations of both the ACIP and the COID are based upon published and unpublished data on disease incidence and severity; risk groups; epidemiology; and the safety, immunogenicity, and efficacy of the vaccine. Issues of implementation involving the vaccine's acceptability to parents and patients, distribution and storage of the vaccine, the administration of the vaccine, and its impact on the healthcare delivery system also are considered. Because financing of vaccines has become an important issue, economic analyses of new vaccine recommendations are important in formulating recommendations. If few deaths and low morbidity outcomes from a vaccine-preventable disease occur, then cost-effectiveness becomes a major consideration. For each vaccine, direct (medical care) and indirect (lost time from work) cost savings are calculated.

Both the ACIP and the COID use specific rules of evidence to judge the quality of data when making decisions about the strength of recommendations (Table 3).[7] Studies that provide the highest quality data are randomized, double-blinded, and placebo-controlled.[8] When inadequate data are available, recommendations may be developed based upon expert opinion.

ACIP

The ACIP and the CDC develop federal vaccine recommendations. The ACIP, created in 1964 under the Federal Advisory Committee Act, provides advice and guidance to the secretary of the Department of Health and Human Services (HHS) and to the director of the CDC on the most effective means to prevent vaccine-preventable diseases. The ACIP develops written recommendations subject to the approval of the CDC director for the routine administration of vaccines to pediatric and adult populations. These recommendations include the appropriate indications, intervals, dosages, and precautions and contraindications applicable to the vaccines. ACIP working groups perform the background work in developing vaccination recommendations. Working groups are composed of several ACIP members and liaisons from the professional societies and from other organizations with an interest in immunization. Working groups review and summarize data for presentation to the entire ACIP. The target populations for ACIP recommendations are the public and private healthcare providers who administer vaccines, the public and private officials who make vaccine policy, and the general public.

The committee consists of 15 regular voting members, including 1 consumer representative. ACIP members are selected on the basis of their expertise and the qualifications necessary to contribute to the fulfillment of the committee objectives. Potential ACIP members are nominated by the CDC to the secretary of the department of HHS and serve 4-year terms if appointed. The ACIP also consists of 19 liaison members who represent medical professional groups and includes 2 members from the COID of the AAP, and 8 ex officio members who represent other federal agencies. Table 4 presents the organizations represented by liaison and ex officio members on the ACIP and COID.

Table 3. Quality of Evidence Used to Establish Vaccine Recommendations

Level of Evidence	
I	Evidence from randomized, controlled trials
II	Evidence from other epidemiologic studies
III	Opinions of authorities
Strength of Evidence	
A	Good evidence to support recommendation
B	Fair evidence to support recommendation
C	Insufficient evidence to support recommendation

Table 4. Organizations with Liaison and Ex Officio Members Represented on the ACIP and the AAP Committee on Infectious Diseases, June 2002

Type of Member	*Organizations Represented on*	
	ACIP	*AAP Committee on Infectious Diseases*
Liaison	American Academy of Family Physicians	American Academy of Family Physicians
	American Academy of Pediatrics	American Thoracic Society
	American Academy of Health Plans	Canadian Paediatric Society
	American College of Obstetricians and Gynecologists	Centers for Disease Control and Prevention
	American College of Physicians	Food and Drug Administration
	American Hospital Association	National Institutes of Health
	American Medical Association	National Vaccine Program Office
	American Pharmaceutical Association	Pediatric Practice Action Group
	Association of Teachers of Preventive Medicine	
	Biotechnology Industry Organization	
	Canadian National Advisory Committee on Immunization	
	Health Care Infection Control Practices Advisory Committee	
	Infectious Diseases Society of America	
	London Department of Health	
	National Immunization Council and Child Health Program, Mexico	
	National Medical Association	
	National Vaccine Advisory Committee	
	Pharmaceutical Research and Manufacturers of America	
Ex officio	Indian Health Service, Department of Health and Human Services	None
	Office of the Assistant Secretary of Defense for Health Affairs	
	Division of Vaccine Injury Compensation, Health Resources and Services Administration	
	Center for Medicaid and State Operations, Health Care Financing Administration	
	National Institute of Allergy and Infectious Diseases, National Institutes of Health	
	Center for Biologics Evaluation and Research, Food and Drug Administration	
	National Vaccine Program Office	
	Department of Veterans Affairs	

Abbreviations: AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices.

Each ACIP member is required to complete financial disclosure forms and to disclose at the beginning of every meeting relevant financial interests that could be conflicts of interest. Persons with conflicts of interest related to specific vaccines are not permitted to vote on any issue concerning that vaccine. Meetings are conducted 3 times per year, and notices of meetings with agenda items are published in the *Federal Register*. ACIP meetings with rare exception are open to the public. ACIP recommendations are reviewed by the CDC and when accepted are published in the *MMWR Morbidity and Mortality Weekly Report*.

After recommendations for use of new vaccines for infants, children, and adolescents have been approved, the ACIP is responsible for defining use of the vaccine under the Vaccines for Children Program (VFC) through passage of separate resolutions. The VFC is an entitlement program that funds the public sector purchase of vaccines for the following groups of persons younger than 19 years of age: 1) Medicaid-enrolled, 2) uninsured, 3) American Indian or Native Alaskan descent, and 4) without insurance to cover immunizations (ie, underinsured) and seeking care at a federally qualified health center. Guidelines for including a vaccine in the VFC program were established by the Omnibus Budget Reconciliation Act of 1993. In 2000, the VFC program purchased approximately 35 percent of distributed vaccines recommended for children and adolescents.

COID

The COID is a standing committee of the AAP. It provides advice and guidance to the board of directors of the AAP on immunization and issues related to infectious diseases that affect infants, children, and adolescents. The target popu-

lations are pediatricians and other healthcare providers who deliver care to children.

The committee consists of 12 voting members, including the chairperson, the editor of the *Red Book*, and 9 liaison members who represent public and private organizations (Table 4). Selection of COID members is based on their expertise and qualifications in the areas of pediatrics, infectious diseases, immunizations, and healthcare delivery. Conflict of interest forms are signed by each COID member. Formal meetings are conducted twice a year. Initial recommendations for vaccines are developed by a subcommittee that reviews and summarizes data for presentation to and discussion by the committee. The recommendations are submitted to the AAP board of directors and, if accepted, are published in *Pediatrics* as academy policy statements.

The harmony that has been achieved for most ACIP and COID vaccine recommendations is because of the close communication that exists between the 2 committees. When recommendations from the committees differ, the differences have been minor. The harmonized recommended childhood immunization schedules are published in January of each year in *MMWR*, *Pediatrics*, and *American Family Physician* and are posted on Web sites (http://www.cdc.gov/nip and http://www.aap.org).

National Vaccine Program

Congress created the National Vaccine Program in 1986 under a section of the Public Health Service Act.

National Vaccine Program Office

This legislation established the National Vaccine Program Office to provide leadership and coordination among federal agencies in working together to fulfill the goals of the National Vaccine Plan. These goals are reflected in a framework that includes goals, objectives, and strategies for the optimal prevention of both infectious diseases through immunizations and adverse reactions to vaccines.

The National Vaccine Program is a collaborative effort of all the groups that have key roles in immunizations. Such groups are federal agencies, the public, states, municipalities, health care providers, and private-sector entities such as vaccine manufacturers. Through the National Vaccine Program these groups undertake their individual activities in a coordinated manner.

The National Vaccine Advisory Committee (NVAC)

The purpose of NVAC is to advise and make recommendations to the director of the National Vaccine Program, the assistant secretary for health in the Department of HHS, on program responsibilities. The committee meets 3 times a year. Its functions are: 1) to study and recommend ways to encourage the availability of an adequate supply of safe and effective vaccination products in the United States; 2) to recommend research priorities and other measures the director of the National Vaccine Program should take to enhance the safety and efficacy of vaccines; 3) to advise the director of the program in implementation of specific sections of the Public Health Service Act; and 4) to identify annually for the director of the program the most important areas of government and nongovernment cooperation that should be considered in implementing relevant sections of the Public Health Service Act.

The NVAC consists of 15 members appointed by the director of the National Vaccine Program in consultation with the National Academy of Sciences. Members are appointed to 4-year terms and are individuals who are engaged in vaccine research or manufacture, physicians, members of parent organizations concerned with immunizations, or representatives of state or local health agencies or public health organizations. The NVAC has 13 additional members: 4 are liaisons representing other federal vaccine advisory committees, and 9 are nonvoting, ex officio members who represent federal agencies whose responsibilities involve immunization programs.

Delivery and Financing

Primary care health providers and parents or guardians have the responsibility for ensuring that children are adequately immunized. For persons without primary care providers, public and hospital-based clinics provide immunizations through federal- and state-funded programs that finance the purchase of vaccines for low-income, uninsured, and underinsured children. In 2000, approximately 50 percent of vaccines administered to children were purchased by the federal government or by state and local governments through negotiated federal contracts. These contracts usually provide discounts of approximately 20 to 50 percent from the catalog prices and are administered through 2 federal programs, the VFC and the Section 317 grant programs. VFC, an entitlement program, supplies vaccines free of charge to enrolled providers for treating eligible children and adolescents. VFC-purchased vaccines are administered by private vaccine providers enrolled in the program or by public clinics. Funds supplied under the Section 317 grant are appropriated annually by the Congress and are distributed by CDC to state and local immunization programs to support immunization for children not covered by VFC. These vaccines are administered in public clinics and by private providers in some states. Approximately 80 percent of vaccines in the United States are administered in the private sector.[9]

The National Immunization Survey (NIS) monitors immunization rates in the recommended childhood immunization schedule through ongoing national estimates of vaccination coverage among 19- to 35-month-old children (median, 27 months) for the 50 states and for 28 selected urban areas.[10,11] Immunization rates with routinely recommended childhood vaccines increased substantially after the Childhood Immunization Initiative was implemented in 1993.[12] In 2000, rates for receipt of 3 doses of diphtheria and

Table 5. Standards for Child and Adolescent Immunization

1.	Vaccination services are readily available.
2.	Vaccinations are coordinated with other healthcare services and provided in a Medical Home when possible.
3.	Barriers to vaccination are identified and minimized.
4.	Patient costs are minimized.
5.	Healthcare professionals review the vaccination and health status of patients at every encounter to determine which vaccines are indicated.
6.	Healthcare professionals assess for and follow only medically accepted contraindications.
7.	Parents/guardians and patients are educated about the risks and benefits of vaccination in a culturally appropriate manner and in easy-to-understand language.
8.	Healthcare professionals follow appropriate procedures for storage and handling of vaccine.
9.	Up-to-date, written vaccination protocols are accessible at all locations where vaccines are administered.
10.	Persons who administer vaccines and staff who manage or support vaccine administration are knowledgeable and receive ongoing education.
11.	Healthcare professionals simultaneously administer as many indicated vaccine doses as possible.
12.	Vaccination records for patients are accurate, complete, and easily accessible.
13.	Healthcare professionals promptly and accurately report adverse events that occur after vaccination to the Vaccine Adverse Event Reporting System (VAERS) and are aware of a distinct program, the National Vaccine Injury Compensation Program (VICP).
14.	All personnel in contact with patients are vaccinated appropriately.
15.	Systems are used to remind parents/guardians, patients, and healthcare professionals when vaccinations are due and to notify those who are overdue.
16.	Office- or clinic-based reviews of patient records and vaccination coverage assessments are performed annually.
17.	Healthcare professionals practice community-based approaches.

Adapted from reference 15.

tetanus toxoids and acellular pertussis vaccine (DTaP), *Haemophilus influenzae* type b (Hib) conjugate, polio and hepatitis B vaccines, and 1 dose of measles-mumps-rubella vaccine (MMR) among children 19 to 35 months of age were 90 percent or greater than for each vaccine separately. Coverage with varicella vaccine, which became commercially available in 1996, was 68 percent.[13] National coverage in 2000 with the combination vaccination series 4:3:1:3:3 (DTaP, polio, MMR, Hib, and hepatitis B) was 73 percent. The major determinant of the combined series is the fourth dose of DTaP.

The immunization status of every child should be assessed each time a child is seen for health care, whether for preventive or curative services. Physicians should ensure that each person has an immunization record and that the record is updated each time an immunization is given. Parents should bring the immunization record to each healthcare visit. Immunization registries, which are intended to compile and make available to all providers the immunization records of all children in a city or state, are being developed; such registries will provide a system whereby reminders about impending or missed immunizations can be generated and providers can gain access to a reliable record for children whose addresses change.[14]

The NVAC has developed "Standards for Children and Adolescent Immunization Practices" to help providers maintain practices that optimize children's immunization status (Table 5).[15] These standards, initially published in 1992 by the NVAC, recently have been revised.[15] The standards are endorsed by medical professional organizations and reflect a largely privatized vaccination delivery system that has improved public financing for susceptible children via the VFC program and an emphasis on adolescent vaccination.

State Laws

Coverage with vaccines included in the recommended childhood immunization schedule among school-aged children and among attendees of child care centers and Head Start programs has been greater than 95 percent since the early 1980s. This achievement is the result of enforcement of comprehensive state immunization laws and regulations requiring receipt of specified vaccines for school or child care attendance. All requirements are state-based; the vaccines that are included, the number of doses required, and other aspects vary slightly by state. Many states have expanded the scope of their school requirements by requiring 2 recently recommended vaccines—hepatitis B and varicella—for school entry (43 states for hepatitis B, and 26 states and the District of Columbia for varicella).

Vaccine Monitoring

Monitoring the effects of vaccination programs and the safety of vaccines is important for refining immunization strategies and for providing assurance to the public and medical community that vaccines are safe. Each state mandates surveillance for vaccine-preventable diseases, and data are compiled in the National Notifiable Disease Surveillance System at the CDC. Data are monitored to assess the effectiveness of the vaccines and of the vaccination program. Physicians are urged to report all suspected cases of vaccine-preventable diseases promptly to their local and state health departments.

Monitoring of adverse events after receipt of vaccination is the joint responsibility of the FDA and CDC. Physicians are required to report certain events that occur after vaccination is administered and should report all suspected adverse reactions after vaccination to the Vaccine Adverse Events Reporting System (VAERS).[16] Forms are available through state health departments and can be obtained by physicians and parents by calling 800-822-7967 or via the Web at http://www.vaers.org/.

Conclusion

The immunization program in the United States is healthy, vibrant, and successful, but it continually faces impediments and challenges. Although immunization coverage with the recommended vaccines remains high, the maintenance of societal health benefits necessitates that high rates of immunization be achieved in each new birth cohort. Immunization among preschool-aged children can be increased using reminders and recalls, providing immunization at every opportunity, and administering multiple vaccines when indicated and possible. Concern about vaccine safety issues must be addressed openly, and associations between vaccines and potential adverse events must be investigated using evidence-based studies. Supplies of vaccine must be guaranteed so that all children and adolescents are protected from the morbidity and mortality associated with vaccine-preventable diseases. New and effective vaccines will need to be incorporated into the childhood immunization schedule. These and other issues will have an impact upon the vaccine delivery systems of the future.

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